Please add the following paragraph on page 10, between complete paragraph 3 and 4, starting on line 23:

--In a further embodiment, the isolate is administered in combination with an immune stimulating compound. There are many immune stimulating compounds which may be administered which are known to one of skill in the art, including, but not limited to, heat shock proteins, bacterial cell wall extracts, and BCG. --.

B2

IN THE CLAIMS

1. **(Amended)** A method for treating cancer in a mammal, comprising:

B3

isolating an urine isolate comprising a pool of molecules larger than about 1000 daltons from a mammal with cancer; and

administering an effective amount of the urine isolate to said mammal with cancer.

REMARKS

The Specification has been amended to provide antecedent basis for Claims 18-19 and 33-34 which were included in the Specification as filed. Although Applicants submit that the claims as filed are part of the Specification, a new paragraph has been added to the Specification. Support for the added paragraph can be found in Claims 18-19 and 33-34 of the Specification as filed. As a result of the Amendment, Claims 1-34 and 70-79 are presented for further examination. The changes made to the Specification and Claims by the current amendment, including **[deletions]** and additions, are shown on an attached sheet entitled **VERSION WITH MAKINGS TO SHOW CHANGES MADE**, which follows the signature page of this Amendment.

Rejection under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-19 and 70-79 under 35 U.S.C. §103(a) as being unpatentable over Rote, et al., (1980), in view of Murphy, et al. (1996) and Nestle, et al. (1998), Ravery (1999), Morales, et al. (1995), and Yedavelli, et al. (1999). More specifically, the Examiner believes that the references teach: a method for the treatment of cancer comprising administering a urine isolate comprising molecules larger than about 1000 daltons, and or APC's and or exosomes from APC's which are co-cultured with said urine isolate.

However, Applicants submit that the references do not render the claimed invention obvious because they do not teach **"a method for the treatment of cancer comprising administering an autologous urine isolate comprising a pool of molecules larger than about 1000 daltons, and or APC's or exosomes from APC's which are co-cultured with said urine isolate"**.

The Prior Art References Teach: Rote et al. teach that when urine is isolated, subjected to concentration by Amicon filtration and a hydrophilic gel, and then dialyzed against PBS, the samples showed the presence of tumor specific urine antigens of MW greater than 1,000,000 daltons which were reactive against human sera from cancer patients. Rote et al does not teach administering these urine antigens for the treatment of cancer. Thus, Rote et al teaches only a purified urine antigen of greater than 1,000,000 daltons not a urine isolate. Rote does not teach a mixture of urine antigens including those as low as 1000 daltons. Nor does Rote teach that this mixture may be used for the treatment of cancer or that APC's and/or their exosomes which have been incubated with them may be used. Nestle teaches vaccination with DC's which have been pulsed with specific autologous tumor antigen peptides which were synthesized. Murphy teaches a clinical trial in which dendritic cells pulsed with one specific antigen - PSMA, and PSMA peptides which were synthesized were administered to cancer patients in saline. Ravery teaches the presence of a particular antigen, PSA in the urine of prostate cancer patients. Neither Nestle, Murphy, or Ravery teaches or suggests the use of **a mixture of** tumor specific antigens from urine, but only a specific purified antigen. **Yadevelli and Morales** teach the use of immune stimulating compounds in the treatment of cancer.

The prior art references do not teach an autologous urine isolate comprising a pool of antigens. Thus, the references do not render the claimed invention obvious because the combination of references does not teach all of the claimed elements. None of the references teach the use of an autologous urine isolate comprising a mixture or pool of molecules larger than 1000 daltons for vaccination, for pulsing dendritic cells, or for production of exosomes from dendritic cells. In addition, none of the references teach administering the various forms of the urine isolate to a patient with cancer. Specifically, there is no teaching that a urine isolate comprising a mixture of molecules larger than 1000 daltons could be used for pulsing dendritic cells and isolating exosomes or injecting into a patient with cancer and producing an immune

response whether specific or non-specific. There is no teaching that a minimally purified mixture from urine could be useful for the treatment of cancer. Urine was used only for the identification of existing cancer and in this context only when looking for one specific antigen. In fact, one of skill in the art would be likely to assume that, once the antigens have been through the body, shunted into the kidneys and excreted in the highly acidic urine, they would no longer be useful for mounting an immune response whether specific or non-specific. Alternatively and in addition, one of skill in the art would know that just because a molecule can be identified by a monoclonal or polyclonal antibody, does not mean that it will remain immunogenic if injected into the body or cultured with APC's/DC's. It only means that the epitope exists.

The use of an autologous mixture of urine antigens provides surprisingly effective results: The references do not render the claimed invention obvious because an autologous mixture of urine antigens provides surprisingly effective results for at least three reasons: 1. "Use of a singular priming antigen to pulse the DCs could also lead to escape variant tumor cell types" (see page 3 of the specification, lines 10-11). 2. A single antigen may only be useful in certain patients who are positive for that antigen (see page 3 of the specification lines 7-8). And 3. Tumor antigens may vary in size from 24,000 daltons to greater than 200,000 daltons. Thus, if only a specific purified single antigen is used, many of these useful tumor antigens will be missed (see page 3 of the specification line 17 through page 4, line 16). Thus, by using a mixture and using autologous urine, it is almost guaranteed that tumor antigens that are useful for the patient will be present and, even more likely, that multiple useful tumor antigens will be present.

Rejection under 35 U.S.C. §103(a)

The Examiner has rejected claims 20-34 under 35 U.S.C. §103(a) as being unpatentable over Rote, et al., (1980), Murphy, et al. (1996) and Nestle, et al. (1998), Morales, et al. (1995), and Yedavelli, et al. (1999) and further in view of Cariuk, et al., (1997). More specifically, the Examiner believes that the combination of Cariuk, et al. which teaches a 24,000 MW antigen which is present in the urine of patients with cachexia with the above-mentioned references renders the claimed invention obvious. However, as explained in the 103 rejection above, the combination of references does not render the claimed invention obvious because they do not teach a mixture or pool of antigens from autologous urine. Thus, because Cariuk et al. only

teaches a single antigen, it does not provide this teaching and the combination with Cariuk et al. does not render the claimed invention obvious.

Conclusion

Should there be any questions regarding the above-captioned patent application, the Examiner is respectfully requested to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: _____ By: _____

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072902

VERSION WITH MAKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please replace the first complete paragraph on page 6, lines 8-12 with the following paragraph:

--The treatments can be performed without costly identification of specific tumor associated antigens, are without serious side effects, can halt cachexia, have a lower likelihood of inducing escape of variant tumor cells, and are potentially useful for a much larger percentage of the population than other immunotherapies which use single, non-autologous molecules, or tumor cell lysates as antigen sources.--.

Please add the following paragraph on page 10, between complete paragraph 3 and 4, starting on line 23:

--In a further embodiment, the isolate is administered in combination with an immune stimulating compound. There are many immune stimulating compounds which may be administered which are known to one of skill in the art, including, but not limited to, heat shock proteins, bacterial cell wall extracts, and BCG. --.

IN THE CLAIMS

1. **(Amended)** A method for treating cancer in a mammal, comprising:

isolating an urine isolate comprising a pool of molecules larger than about 1000 daltons from a mammal with cancer; and

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